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Tetrahedron Letters 44 (2003) 1007–1010

TETRAHEDRON
LETTERS

Regioselective allylation reactions using crotyl Grignard reagent–$CeCl_3$ systems

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Received 18 October 2002; revised 20 November 2002; accepted 29 November 2002

Abstract—Regioselective allylation reactions using crotyl Grignard reagent–$CeCl_3$ systems are described. Regioselectivity depends on the lanthanide salts: α-product was predominantly produced with light rare earth elements such as La, Ce, Pr, Nd, whereas γ-product was formed when heavy rare earth elements were used. © 2003 Elsevier Science Ltd. All rights reserved.

The reactions in Grignard reagents–$CeCl_3$ systems with carbonyl compounds have become important carbon–carbon bond forming reactions in organic synthesis because these combined reagent systems effectively suppress undesired reactions such as enolization, reduction, condensation, conjugate addition, and pinacol coupling.[1,2] Although reported examples using this system number in the hundreds, the mechanisms underlying these reactions remain unclear. In order to gain insight into the mechanism of the generation of the reactive intermediates, allylation reactions using crotyl Grignard reagent–$CeCl_3$ systems were examined. Allylation reactions represent one of the most fundamental carbon–carbon bond forming reactions in modern organic synthesis.[3] In general, reactions involving unhindered carbonyl compounds with substituted allylic organometallic reagents such as M = Li, Mg, Cu, Zn, Cd, B, Al, Si, Sn, Ti, Zr, Cr, and Mn result in the predominant formation of γ-adducts in which the allylic group is attached at the more highly substituted position. On the other hand, α-selective allylation reactions are also of great importance and to date, a number of important studies have been carried out. For example, it has been reported that allylic organometallic reagents such as M = Mg–$AlCl_3$,[4] SPh–LDBB–$CeCl_3$,[5] Ba,[6] Sn–$CoCl_2$,[7] yield α-adducts.[8] We report herein regioselective allylation reactions of carbonyl compounds using crotyl Grignard reagent–$CeCl_3$ systems.

We examined allylation reactions that use crotyl Grignard reagents with benzaldehyde in the presence of various lanthanide salts. Reactions were carried out via an addition of crotyl Grignard reagent to a suspension of dry lanthanide salt in THF at 0°C. After 30 min, benzaldehyde was added to the reaction mixture at −78°C. The reaction was monitored by TLC. Hydrolytic work-up with 3% AcOH, followed by column chromatography, afforded the allylated product. Results are summarized in Table 1 and Figure 1. Regioselectivity could be classified into three groups based on increasing atomic number. A high level of α-regioselectivity was observed with light rare earth elements such as La, Ce, Pr and Nd. The configuration of α-adducts was highly stereoselective for the *trans* conformation. Gd, Tb, Dy and Ho afforded the α-product to a medium degree. In contrast, γ-regioselectivity was observed when heavy rare earth elements: Er, Tm, Yb and Lu were used. $YbCl_3$, in particular afforded the γ-product almost exclusively. It is noteworthy that high level of γ-regioselectivity was also observed when $ScCl_3$ was used.

In order to clarify the origin of this selectivity, the structure of reactive species in these reactions was investigated. Tsutsui,[9] Wu,[10,11] Brunelli,[12] and Evans[13] independently reported on the synthesis and structure of the allyllanthanide complexes: $Cp_2LnC_3H_5$,[9] $Ln(C_3H_5)_5Li_2$,[10] $(C_3H_5)_5LnCl_5Mg_2(tmed)_2$,[11] $Ln(C_3H_5)_4$-Li,[12] and $Cp^*_2LnC_3H_5$.[13] Each structure has been shown to possess a η^3-allyl moiety using IR and/or X-ray analysis. We then attempted to isolate the reactive species of this reaction. Allyl or crotyl Grignard reagent was added to a suspension of dry $CeCl_3$ in THF at 0°C. After stirring for 30 min, the resultant

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Keywords: allylation; cerium and compounds; Grignard reagents; regiocontrol.

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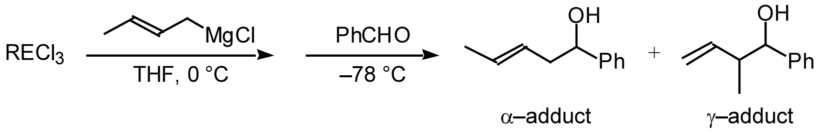
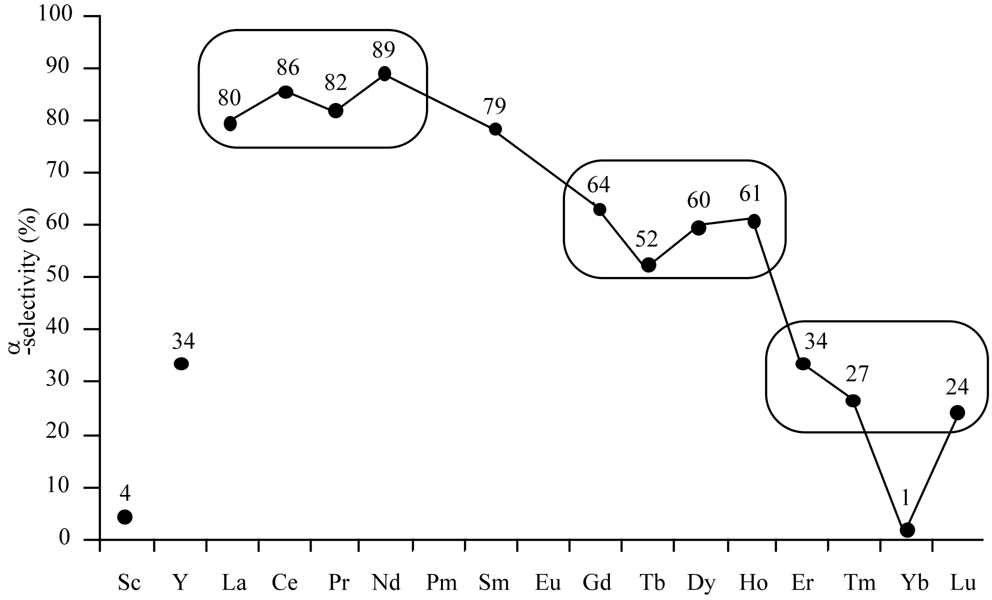
PII: S0040-4039(02)02741-7

Table 1. Regioselective allylation reactions of benzaldehyde by using crotyl Grignard reagent–rare earth chloride systems[a]



RE	yield (%)[b]	α(*cis*/*trans*) : γ[c]	RE	yield (%)[b]	α(*cis*/*trans*) : γ[c]
Sc	89	**4** : 96	Gd	96	**64**(4/96) : 36
Y	95	**34**(7/93) : 66	Tb	97	**52**(23/77) : 48
La	93	**80**(25/75) : 20	Dy	98	**60**(5/95) : 40
Ce	94	**86**(13/87) : 14	Ho	92	**61**(8/92) : 39
Pr	89	**82**(21/79) : 18	Er	94	**34**(9/91) : 66
Nd	98	**89**(8/92) : 11	Tm	91	**27**(17/83) : 73
Sm	99	**79**(4/96) : 21	Yb	88	**1** : 99
Eu	trace		Lu	91	**24**(16/84) : 76

[a] All reactions were carried out in THF for 1 h with a molar ratio of 1 : 1.5 : 1.5 (carbonyl compound/Grignard reagent/$RECl_3$). [b] Combined yield of α– and γ–isomer. [c] The ratio was determined by ^{1}H NMR analysis.



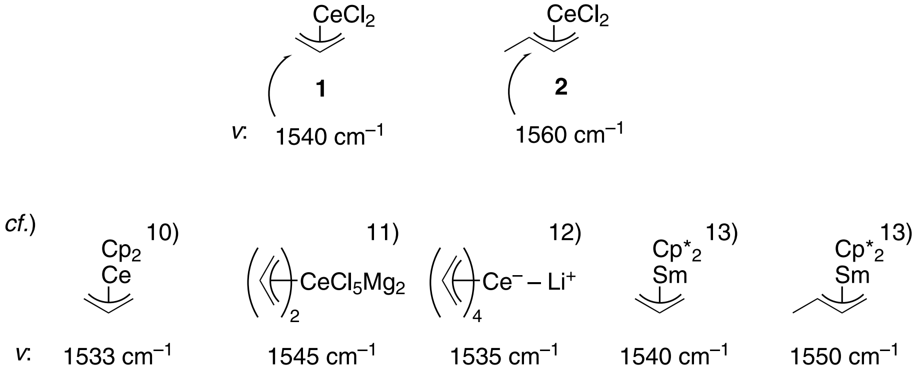
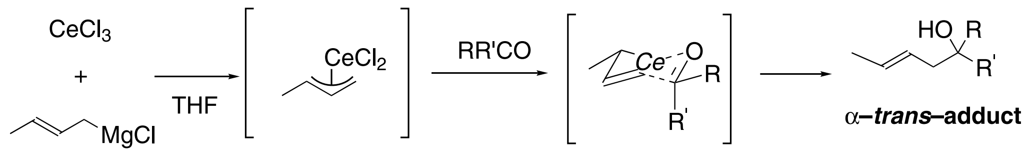


Figure 1.



Scheme 1. A plausible mechanism of the regioselective allylation reaction.

mixture was allowed to stand for 10 h at room temperature and the supernatant was transferred to a centrifuge tube. After centrifugation, the supernatant was taken up and evaporated to give a dark brown powder.[14] Although, X-ray analysis was unsuccessful, structural information was obtained from the IR spectra. The IR spectra of **1** and **2** in Nujol mulls show bands at 1540 cm^{-1} for **1** and 1560 cm^{-1} for **2**, which could be assigned to the delocalized C–C stretch characteristic of η^3-allyl moieties, according to the reported IR spectra of the above allyllanthanide complexes (Fig. 1). In contrast, the intermediate prepared from $\mathrm{YbCl_3}$ was obtained as a white powder and the IR spectra did not show any bands at 1540–1560 cm^{-1}. These results suggest that the reaction intermediate prepared from $\mathrm{CeCl_3}$ is an η^3-allyl lanthanide complex, whereas that prepared from $\mathrm{YbCl_3}$ is an another species. It is well known that Sc(III) and Yb(III) have exceptionally high catalytic activities in numerous Lewis acid-catalyzed reactions.[15] Their high Lewis acidities prevent transmetallation due to strong M–Cl bonds. The model reaction was examined using dibenzylketone and *n*-BuMgBr. The addition products were obtained in excellent yields (98%) with $\mathrm{CeCl_3}$. On the other hand, combined use of $\mathrm{YbCl_3}$ and *n*-butylmagnesium bromide resulted in a lower yield (24%), probably because of sluggish transmetalation.

A plausible mechanism of this regioselective allylation reaction is shown in Scheme 1. Transmetallation of crotyl Grignard reagent to $\mathrm{CeCl_3}$ via the $\mathrm{S_E2'}$ process results in an η^3-allylcerium species. Carbonyl compounds react with the η^3-allylcerium species at a sterically less hindered site to give the α-allylated product.

In summary, we have demonstrated regioselective allylation reactions using crotyl and prenyl Grignard reagent–$\mathrm{CeCl_3}$ systems. Regioselectivity was found to depend on the lanthanide salts. The structures of the intermediates were investigated based on IR spectra, and the η^3-allylcerium complex is suggested. These results indicate that the organocerium species, written as '$\mathrm{RCeCl_2}$', are produced from Grignard reagent and $\mathrm{CeCl_3}$, and is one of the active species in Grignard reagent–$\mathrm{CeCl_3}$ systems.

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